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Sulfadoxine–pyrimethamine alone or with azithromycin for the intermittent preventive treatment of malaria in pregnancy: protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction Increasing *Plasmodium* resistance levels to sulfadoxine–pyrimethamine (SP) threaten the effectiveness of intermittent preventive treatment in pregnancy (IPTp) and have prompted the evaluation of alternative strategies. Azithromycin (AZ) could have add-on effects on malaria and treat sexually transmitted infections (STIs), both conditions described as major causes of adverse pregnancy outcomes (APO). Inconsistent findings on the utility of AZ for the prevention of APO were reported; however, thus far, no comprehensive meta-analytic synthesis of data has been published. This review aims to investigate the effects of SP+AZ administered in women as IPTp on the risk of low birth weight in malaria-endemic areas.

Methods and analysis Eligible studies will be identified through a pre-established search strategy in several electronic databases (Medline, Cochrane Library, Web of Science, EMBASE, WHO International Clinical Trials Registry Platform, ClinicalTrials.gov and AJOL) and will comprise peer-reviewed papers reporting original data on the effects of SP+AZ on the risk of APO. Only randomised controlled trials published until 30 September 2024 in English or French will be included. IPTp with SP+AZ regimens (intervention) will be compared with IPTp with SP alone or with a placebo (control). As primary outcomes, data on the frequency of low birth weight will be collected. Secondary outcomes include the rates of stillbirth, preterm birth, miscarriage and neonatal death. Data will be extracted independently by two reviewers using a predefined extraction form. If the data quality allows for quantitative synthesis, a fixed-effects meta-analysis will be conducted if there is low inter-study heterogeneity. Otherwise, the random-effects meta-analysis will be conducted to take into account uncertainty in pooled estimates that could be due to inter-study heterogeneity. The review protocol was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocols (PRISMA-P) guidelines.

Ethics and dissemination Ethical clearance is not needed as the data will be from already published studies in which informed consent and ethical approval were obtained by primary investigators. Our dissemination plan includes the publication in a peer-reviewed journal as well as conference presentations.

PROSPERO registration number CRD42020149592.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Only randomised controlled clinical trials will be included to provide unbiased estimates of treatment effects.
⇒ All published high-quality data will be included to generate up-to-date and reliable evidence to inform policy-making and advocate best practices.
⇒ Differences in the outcome definition and measurement may cause challenges in data pooling and drawing conclusions.

INTRODUCTION

Of the 2.6 million stillbirths[1] and 2.7 million neonate deaths[2] occurring each year worldwide, nearly half are reported in Sub-Saharan Africa (SSA).[3 4] Low birth weight (LBW; <2 500 g) secondary to intrauterine growth retardation or preterm delivery[5] is singled out as the most important contributing factor to neonatal mortality in SSA.[6 7] Indeed, in this region, more than 80% of neonatal mortality occurred in infants born with LBW.[8] Noteworthy, those who survived remain at a higher risk of short- to long-term adult-prone conditions such as stunting,[9] low intelligence quotient (IQ < 70)[10] and chronic conditions including type 2 diabetes.[11]

Malaria in pregnancy (MiP) and sexually transmitted infections (STIs) are identified as key factors of LBW.[6 12] While malaria mainly causes intrauterine growth retardation,[13] STIs are responsible for intrauterine infections that commonly lead to premature delivery.[14] Both infections are endemic and highly prevalent in SSA.[13 15] For instance, up to 100 000

newborn LBW and up to 6% of neonate deaths would be prevented if adequate malaria prevention measures were adopted.[6]

For the prevention of MiP, the WHO recommends the use of IPTp with sulphadoxine–pyrimethamine (SP) starting from the second trimester of pregnancy with an interval of at least 4 weeks between doses and requires a minimum of three doses until delivery.[16] However, increased *Plasmodium falciparum* resistance to SP is waning the efficacy of the IPTp-SP to adequately prevent malaria and its related consequences on the pregnancy outcome and has prompted the evaluation of alternative strategies.[17] In SSA, STI management in pregnancy is mainly based on a syndromic approach during which a group of symptoms is identified, and efficacious antibiotics are provided by following a simplified algorithm.[18] However, these infections are frequently asymptomatic during pregnancy, which alters the sensitivity of the syndrome-based approach.[19] Thus, alternative interventions are also needed to improve the prevention of their negative effects on the mothers and their babies.

Systematic delivery of AZ, a broad-spectrum macrolide medicine with antibiotic, antimalarial and antiviral properties,[20] to pregnant women, even given once, provided promising results in reducing APOs.[21 22] In addition, AZ was reported to be comparable to SP for IPTp in a study conducted in SSA.[23] Its adjunction to SP could potentially provide additional benefits for preventing both malaria and STIs. Thus, several studies were conducted to assess the efficacy of SP+AZ regimens for IPTp to prevent APOs. However, inconsistent findings were reported and have hampered adequate decision-making. For example, in Malawi, although Lutamo et al reported significant reductions in the incidence of preterm deliveries and LBW,[24] Van den Broek et al did not report any significant effects in the same country.[25] So far, no comprehensive analytic evaluation has been published. We propose to undertake a systematic review and meta-analysis to investigate the risk of APOs among pregnant women who received SP+AZ (intervention) compared with SP alone (control). The results of the review will be useful in generating evidence to inform decision-making.

Objective

This review aims to investigate the effects of SP+AZ administered to women as IPTp on the risk of LBW and other APOs, including preterm birth, stillbirth, miscarriage and neonatal death in malaria-endemic areas.

METHODS AND ANALYSIS

Protocol design and registration

This systematic review and meta-analysis study will summarise and synthesise available evidence published until 30 September 2024. This design is adequate for pooling research results to inform decision-making and advocate best practices by integrating results from several original studies.[26] The development of this study protocol was in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis Protocol (PRISMA-P) (online supplemental appendix 1).[27 28] The study protocol is registered with the International Prospective Register of Systematic Reviews database (PROSPERO), a platform for the international registration of prospective systematic reviews,[29] and assigned the registration number CRD42020149592.

Study eligibility criteria

Type of study

To be included, studies should meet the following criteria: (1) parallel-group randomised controlled trials (RCTs) in pregnant women and (2) report on adverse pregnancy outcomes. All other types of trials will be excluded to avoid biases related to non-randomised and non-controlled trials. Also, eligible studies with unclear reporting of APOs, those using secondary data, and studies with pre-delivery administration of AZ or during the first trimester of pregnancy will be excluded.

Study participants

The participants are pregnant women residing in malaria-endemic transmission areas who received intermittent preventive treatment of malaria in pregnancy.

Intervention

The experimental intervention consists of oral SP+AZ.

Comparator

The control is the current standard of care for the IPTp with SP alone or with a placebo.

Period

Only studies published until 30 September 2024 will be considered. The time frame is proposed for convenience to capture all available evidence that could be sufficient to draw adequate conclusions.

Type of outcome measures

Primary outcome

The main outcome of interest will be the incidence of LBW (<2 500 g) regardless of gestational age.[5]

Secondary outcomes

Secondary outcomes will include miscarriage (loss of pregnancy before 28 weeks of the completed gestation period),[30] stillbirth (loss of pregnancy after 28 weeks of gestation),[30] preterm birth (delivery before 37 weeks of gestation)[31] and neonatal death (death of live neonates within 28 days of life).

Search strategy and databases

A search strategy was developed using key concepts in the research question. A concept map was established using keywords and medical subject headings (MeSH) such as azithromycin, pregnancy, Africa South of the Sahara and similar terms such as azithromycine or sub-Saharan Africa. We will conduct a comprehensive database search including Medline, Cochrane Library, Web

of Science, EMBASE, WHO International Clinical Trials Registry Platform, ClinicalTrials.gov, and the African Journals Online (AJOL), with a combination of MeSH terms and keywords within the research equation with Boolean connectors (AND, OR, and NOT). To ensure a comprehensive search of appropriate electronic databases, certain text words were truncated to enable the retrieval of relevant articles that might have used different spellings for the same word. The draft of the search strategy for PubMed is as follows: ("azithromycin"(MeSH Terms) OR "azithromycin"(All Fields) OR "azithromycin*"(All Fields)) AND (Malaria(MeSH) OR Malaria(All Fields)) AND ("pregnancy"(MeSH Terms) OR "pregnancy"(All Fields)). This search strategy will be subsequently modified to adapt to the requirements of other databases. Google Scholar will be searched to further identify grey literature. A pre-test of the search strategy will be performed by reviewer SO in PubMed and verified by TR between 10 and 14 August 2024. On 1 October 2024, TR will implement the electronic searches. Bridging searches will be conducted to capture literature published between October 2024 and the final review submission. Searches will be limited to articles published or abstracted in English or French.

Data extraction and management

Studies selection

Records found by this search equation will be uploaded on Rayyan QCRI, the Systematic Reviews web app, to identify duplicate documents and subsequently screen for relevant titles and abstracts by two independent reviewers (ML and SO).[32] If there is any disagreement between ML and SO, consensus will be based on discussion whenever possible. If still no agreement is reached, TR will decide on the eligibility. The full texts of relevant papers identified and their reference lists will be scanned to identify additional articles. An ID will be assigned to each eligible study for summarising purposes.

Data extraction

An electronic data extraction form was developed by ML based on the Cochrane Collaboration data collection form for randomised controlled trials and was peer-reviewed by all the members of the research team (online supplemental appendix 2). Two reviewers (SO and TR) pilot-tested this extraction form with two randomly selected trials, and we will adapt and apply the extraction form to all included publications. Two reviewers (SO and ML) will independently extract the following variables from the studies included:

- Publication details: authors' details, year of publication and authors' contact.
- Eligibility: confirm eligibility for review and the reason for exclusion.
- Methods: study design, study site, total duration, sequence generation, allocation and concealment and blinding.
- Participants: total number, sociodemographic, ethnicity, settings, age, country, gravidity and comorbidity.
- Intervention: specific intervention, intervention details (number and timing of doses and dosage) and integrity of intervention.
- Outcomes: outcome, timepoint collected, timepoint reported, unit of measurement and tool of outcome measurement.
- Results: total sample size and per group, missing participants and number of events observed.
- Miscellaneous: funding source, key conclusions of study authors and miscellaneous comment by the review author.

In case of missing data, corresponding authors will be contacted through their provided email address with a maximum waiting time of 30 days and three email attempts. In the case of multiple reports on a single study, they will be compared independently by two reviewers (SO and ML) using author names, study locations, intervention characteristics, date and duration of the studies and sample sizes at baseline, as recommended by the Cochrane Handbook,[33] and only one entry will be included to avoid biases related to multiple inclusions of the same trial.

Quality assessment

Each included study quality will be assessed based on the Grading of Recommendations Assessment, Development and Evaluation system.[34] The following domains will be examined for each outcome: inconsistency, indirectness, imprecision, risk of bias and publication bias. Each study will be classified as high, moderate, low or very low quality of evidence.

Risk of bias in the individual studies

The risks of bias for each study will be assessed by two reviewers (ML and SO) using the revised Cochrane risk-of-bias tool for randomised trials (RoB 2).[35] The following aspects will be analysed: random sequence generation, concealment of allocation, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other biased. Each source of risk will be graded as low, high or unclear risk of bias. A study will be considered at low risk of bias if randomisation sequence generation, blinding and outcome data reporting are adequately performed and reported.

Assessment of heterogeneity

To test heterogeneity among studies, the index of inconsistency (I^2) will be calculated.[36] The I^2 statistic describes "the percentage of total variation across studies that is due to heterogeneity rather than chance".[36] An I^2 value >50% indicates the presence of significant statistical heterogeneity.

Test for publication bias

We will assess publication bias, the tendency of reporting studies with expected outcomes or studies, which

demonstrate significant findings graphically using a funnel plot (a plot of effect estimates against sample sizes). Based on the shape of the plot, a symmetrical shape will be interpreted as the absence of publication bias, whereas an asymmetrical shape will be interpreted as the presence of publication bias.[37] In addition to the graphical representation, Egger's regression analysis will be conducted, with a p-value<0.10 indicating publication bias.[38]

Measures of intervention effects

If a quantitative synthesis is possible, the results will be summarised for each outcome. Odd ratios (ORs) will be estimated using the fixed-effects model for data pooling if statistical heterogeneity is low. Otherwise, the random-effects meta-analysis model will be considered to take into account uncertainty in pooled estimates that could be due to inter-study heterogeneity.[33] Individual study and pooled effects will be assessed at 95% CI as well as the pooled effect.

Data synthesis and analysis

Estimates of the pooled intervention effects will be conducted using meta-analysis. If significant inter-study heterogeneity is detected, the random-effects model will be used to provide more appropriate estimates of the pooled effects. The Cochran–Mantel–Haenszel method for dichotomous data will be used to estimate the ORs. Statistical analysis will be conducted using the R statistical package (R Core Team, 2021), RStudio (Rstudio Team, 2023) and the package "meta".[39] Significance level was set at $p < 0.05$.

Subgroup and sensitivity analyses

Subgroup and sensitivity analyses will be performed to assess potential heterogeneity. Sensitivity analysis to assess the reliability of the estimates of the pooled effects will be conducted by excluding trials with a high risk of bias or those reporting missing data. We will conduct subgroup analyses according to the following:

1. Number of AZ doses received (single dose, two doses, and three or more doses).
2. Timing of the administration of the first dose of AZ (second or third trimester).
3. Gravidity: primigravidae, secundigravidae or multigravida.
4. Patient age groups (categorising trials into 18–30 and above 30 years).

Patient and public involvement

None.

ETHICS AND DISSEMINATION

There will be no need for ethical approval as all primary studies in this review are already available in the public domain. However, only studies ethically approved before they were implemented will be considered. Findings of this review will inform decision-making in malaria-endemic settings. Results will be published in a peer-reviewed journal and presented in scientific conferences.

Amendments

In the case of protocol amendments, the date, rationale and description will be provided.

Protocol registration

This review and meta-analysis protocol was registered with PROSPERO (registration number: CRD42020149592).

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Contributors ML and SO conceptualised the study and designed the protocol. TR drafted the search strategy and adapted searches across different electronic databases. ML and SO revised the search strategies. HS, IV, SS and HT provided guidance to the development of the protocol and critically revised the manuscript. ML drafted the original manuscript. TR, MS, SS and SO reviewed and critically revised the manuscript. All authors read and approved the final manuscript. ML is the guarantor of the manuscript.

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